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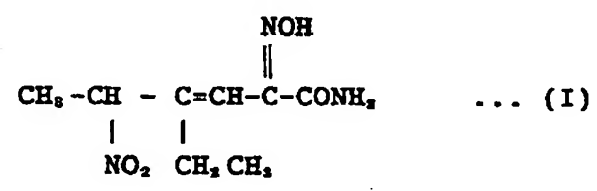
EUROPEAN PATENT APPLICATION

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Stabilizer for 4-ethyl-2-hydroxyimino-5-nitro-3-hexenamide-containing preparation, stabilizing method therefor and drug stabilized thereby.

A stabilizer for 4-ethyl-2-hydroxyimino-5-nitro-3-hexenamide represented by the following chemical formula (I) or a salt thereof acceptable as drug or drug containing as pharmacologically active ingredient a compound represented by a chemical formula (I). In particular, (±)-(E)-4-ethyl-2-[(E)-hydroxyimino]-5-nitro-3-hexenamide or salt/s thereof acceptable as drugs, a stabilizing method by the use thereof and drugs containing such stabilizer and stabilized thereby.



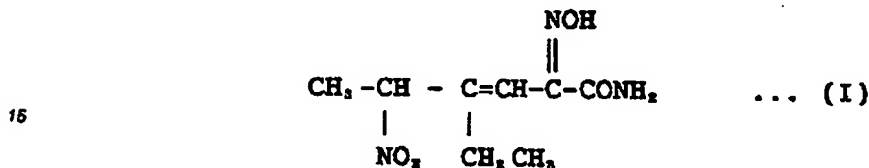
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BACKGROUND OF THE INVENTION

Field of the Invention

5 The present invention relates to a stabilizer for 4-ethyl-2-hydroxyimino-5-nitro-3-hexenamide represented by the following chemical formula (I), in particular, (\pm)-(E)-4-ethyl-2-[(E)-hydroxyimino]-5-nitro-3-hexenamide or a salt thereof acceptable as drug or drugs containing as pharmacologically active ingredient the above compound, a stabilizing method by the use thereof and drugs containing such stabilizer and stabilized thereby.

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20 Description of the Prior Art

It is well known from Japanese Laid-open Patent Publication No. 59-152388 that (E)-4-ethyl-2-hydroxyimino-5-nitro-3-hexenamide or its salt/s accepted as drug has pharmacological activity as a vasodilating drug, anti-thrombotic drug, drug for angina pectoris or the like and, it is disclosed in the
 25 aforementioned publication that this compound can be manufactured as drugs in form of tablet, capsule, pellet, suppository and the like and that various excipients can be used in the manufacture thereof. Through further studies it has been confirmed that the aforementioned compound, in particular, (\pm)-(E)-4-ethyl-2-[(E)-hydroxyimino]-5-nitro-3-hexenamide or a salt has a excellent pharmacological activity. Since this compound is called FK409 by this applicant and about its clinical studies are now under way, the compound to be
 30 stabilized by the method of the present invention will hereinafter be represented by this name.

SUMMARY OF THE INVENTION

FK409 is poor in stability and when, for instance, it is left standing at 40 °C for 2 months, it is
 35 completely decomposed to a dark brown fused substance with its pharmacological activity lost. For manufacture of drugs in some of the aforementioned forms it has to be mixed with proper excipients but when mixed with an excipient, it is extremely poor in stability and the content of the active ingredient is markedly reduced when it is left standing for 1 month at 40 °C.

The present invention has been made for improvement in this respect and is aimed at provision of a
 40 stabilizer effective for preventing decomposition of FK409 and having its pharmacological activity kept for a long period. Another object of the present invention is provision of a method of stabilizing FK409 or drugs containing it as the pharmacologically active ingredient. Still another object of the present invention is to provide a stabilized FK409 or drugs containing it as the pharmacologically active ingredient.

45 DETAILED DESCRIPTION OF THE INVENTION

The stabilizer of the present invention is characterized in that it comprises one or more of group of polybasic acids, fatty acids with a carbon number of 16-20, ascorbic acid, erythorbic acid and riboflavin and the method of the invention is characterized in that stabilization is attained by mixing the aforementioned
 50 stabilizer in drugs containing FK409, and the stability of FK409 as a pharmacological ingredient is markedly improved and FK409-containing drugs excelled in durability of activity are obtained. The present inventors studied various compounds to see their stabilizing effect, that is, to see if they are effective for preventing decomposition of FK409, and as a result discovered that compounds selected from a group of polybasic acids, fatty acids 16-20 in carbon number, ascorbic acid, erythorbic acid and riboflavin have excellent
 55 stabilization effect. As polybasic acids may be cited dibasic acids such as tartaric acid, aspartic acid, succinic acid, malic acid, fumaric acid, maleic acid, malonic acid and glutaric acid, tribasic acid such as citric acid or anhydrides thereof. When the above exemplified polycarboxylic acid has an asymmetric carbon atom(s) such as tartaric acid, malonic acid or citric acid, each of D-form, L-form or racemic mixture

may be used.

As fatty acids 16-20 in carbon number may be cited saturated fatty acids such as palmitic acid, heptadecynoic acid, stearic acid, nonadecanoic acid and arachic acid, and unsaturated fatty acids such as undecylic acid, oleic acid and elaidic acid. Of these, particularly excelled in stabilization effect are
 5 oxydicarboxylic acids such as tartaric acid and their anhydrides, stearic acid as a saturated fatty acid with a carbon number of 18 in the group of fatty acids 16-20 in carbon number, ascorbic acid (vitamin C), erythorbic acid, riboflavin (Vitamin B2), etc. The salt of FK409 may be pharmaceutically acceptable salt including organic or inorganic salt.

As to the quantity of the aforementioned compound to be added as stabilizer, there is no limitation but
 10 it is preferred to be not less than 0.1 weight %, more preferably in a range of 0.3-5 weight %, of the quantity of FK409.

The drug composition of the present invention can be mixed with organic or inorganic carriers or excipients suited for external, oral or non-oral administration so as to be usable as solid, semisolid or liquid medical preparations containing the effective substance of the invention. The invented effective substance
 15 (ingredient) may be mixed with any of the ordinary, nontoxic carriers permitted for medical use and suited for preparation of tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions and the like. As such carriers may be cited water, dextrose, lactose, gum arabic, gelatin, mannitol, starch paste, magnesium silicate, talc, corn starch, keratin, colloid silica, potato starch and urea in solid, semisolid or liquid form, being suited for drug manufacture, and auxiliaries, stabilizers, thickeners, colorants and aromatics are also
 20 usable. It is also possible to use preservatives or bacteriostats for stably maintaining the activity of the drug or its effective ingredient in any given form. The medical composition of the invention is also usable for manufacture of persistent drugs of various forms. It is also possible to use the aforementioned drugs as long lasting drugs of various forms.

FK409 is poor in stability when mixed with an excipient for drug manufacture and its activity is lost
 25 quickly when the mixture is kept in stock at a high temperature, but its decomposition is markedly prevented when one of the aforementioned compounds is added as stabilizer for the resultant preparation or drug to be highly improved in durability of pharmacological activity.

The FK409 content of a drug of the present invention may be determined properly with the stage of the disease the drug is prescribed for and its form, if the desired therapeutic effect could be attained.

In applying the drug of the invention to human being, it may be prepared in various forms suited for
 30 venous or muscular injection, cutaneous administration as in the case of plaster or suppository or oral administration. The dosage depends on the stage of disease and the age of the patient but, generally, the effective dose of FK409 is approx. 0.1-100 mg/kg a day and normal per-time dose is 10 mg, 50 mg, 100 mg or 250 mg on the average.

Example

The composition and effect of the drug of the present invention will be specifically described below with reference to the cited example, but it is to be understood that this invention is not limited to the example
 40 described below.

First the stability of FK409 when it was kept in a capsule, when it was stored mixed with an excipient and when it was mixed with tartaric acid as stabilizer (the residual percentage of FK409) was studied. In the experiment, however, the individual samples were put in #1 bottles, the filled bottles were then sealed, kept at the predetermined temperature and upon lapse of the predetermined time, the residual percentage of
 45 FK409 was measured by the liquid chromatographic method and its proportion to the initial content was determined.

The compositions of the individual samples are shown in Table 1 and the results in Table 2.

Table 1

5		Recipe No.	1	2	3	4
	Composition (mg)	FK409	3	3	3	3
		Lactose	-	87	84	-
10		D-Mannit	-	-	-	84
		DL-Tartaric acid	-	-	3	3
15		Total	3	90	90	90

Table 2

20				Residual percentage (%)			
25				Recipe 1	Recipe 2	Recipe 3	Recipe 4
	original powder of FK409			100	100	100	100
30	Storage condition	40°C	1 month	0	0	95.3	98.6
			3 months	-	-	82.4	99.1
35		Room temp.	6 months	0	0	96.1	100

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As seen from Tables 1 and 2, FK409, either in the form of original powder (recipe No. 1) or mixed with an excipient (recipe No.2), totally loses its pharmacological activity after storage for 1 month at 40 °C, but when a proper dose of tartaric acid is added (as stabilizer), decomposition of FK409 is markedly prevented and its residual percentage is largely increased.

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Table 3 below is given to show the result of study about various compounds on their stabilizing effect on the original powder of FK409.

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Table 3

	Stabilizer dose(g)	Storage condition and residual (%)			
		40 °C	50 °C	60°C	60°C
		1 month	1 month	18 days	7 days
FK409					
Original powder	-	0	0	0	99.3
DL-Tartaric acid	1	97.2	98.0	88.1	99.0
Stearic acid	1	99.3	95.2	-	-
Vitamin C	1	97.1	98.3	87.8	99.0
Erythorbic acid	1	96.3	98.4	83.5	99.8
Vitamin B2	1	97.3	93.9	-	96.0
DL-Malonic acid	1	98.9	83.5	32.5	90.1
DL-citric acid anhydride	1	70.1	76.3	-	-

The dose of stabilizer in g is per 1 g of the original powder of FK409.

As is apparent from Table 3, the compounds used in this experiment all have excellent stabilizing effect on FK409, DL-tartaric acid, stearic acid, vitamin C and erythorbic acid in particular.

The storage conditions in this experiment are rather severe ones, one month of storage at 50 °C being equivalent to storage at the room temperature for approx. 12 months and, this taken into consideration, the effect of this invention is truly outstanding.

Then, the stabilizing effect of tartaric acid on tablets with FK409 as active ingredient will be demonstrated.

The ingredients in the recipe shown Table 4 except only magnesium stearate were mixed, 40 ml of water was added to the mixture (approx. 135 g) and the wetted mixture was uniformly kneaded, vacuum dried and granulated. To the granules the prescribed amount of magnesium stearate was added and, after mixing, the mixture was made into tablets 7mm in diameter by the use of a tablet making machine.

40 tablets thus obtained were put in a #3 bottle, the filled sealed bottle was stored for the predetermined period at the room temperature (25 °C) or 40 °C, and then the residual percentage of FK409 was studied.

The result was as shown in Table 5, and from the tabulated data it is apparent that tartaric acid has an excellent stabilizing effect on FK409 even when it is prepared in tablet form.

Table 4

Recipe No.		1	2	3	4
Composition (mg)	FK409 (Pharma. ingredient)	10	40	10	40
	DL-Tartaric acid (stabilizer)	3	12	3	12
	D-Mannit	107.95	68.95	107.95	68.95
	ECG 505	12	12	-	-
	Ac-Di-Sol	-	-	12	12
	TC-5E	1.35	1.35	1.35	1.35
	Magnesium stearate	0.7	0.7	0.7	0.7
Total		135	135	135	135

ECG 505: Carboxyl methyl cellulose calcium (disintegrator)

Ac-Di-Sol: Crosslinked-carboxyl methyl cellulose-sodium
(disintegrator)

TC-5E: Hydroxy propyl methyl cellulose (binder)

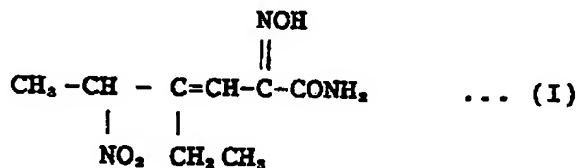
Magnesium stearate (lubricant)

Table 5

			Residual percentage (%)			
			Recipe 1	Recipe 2	Recipe 3	Recipe 4
	Initial		100.0	100.0	100.0	100.0
	Storage condition	40 °C				
		1 month	98.9	100.0	99.9	100.0
		6 months	96.8	97.3	95.1	95.8
		Room temp.				
		1 month	100.0	99.9	99.3	100.0
		6 months	99.2	99.8	99.3	99.6

Claims

1. A stabilizer for 4-ethyl-2-hydroxyimino-5-nitro-3-hexenamide represented by the following chemical formula (I) or a salt thereof acceptable as drug or drug containing as pharmacologically active ingredient a compound represented by the chemical formula (I) or a salt thereof acceptable as drug, wherein said stabilizer is one or more selected from a group of polybasic acids, fatty acids 16-20 in carbon number, ascorbic acid, erythorbic acid and riboflavin.



2. A stabilizer according to claim 1 wherein said 4-ethyl-2-hydroxyimino-5-nitro-3-hexenamide is (±)-(E)-4-ethyl-2-[(E)-hydroxyimino]-5-nitro-3-hexenamide.
3. A stabilizer according to claim 1 or 2, wherein said polybasic acid is oxydicarboxylic acid.
4. A stabilizer according to claim 3, wherein said oxydicarboxylic acid is tartaric acid.
5. A stabilizer according to claim 2, wherein said fatty acid 16-20 in carbon number is a saturated fatty acid.
6. A stabilizer according to claim 5, wherein said saturated fatty acid is stearic acid.
7. A stabilizing method for a compound represented by a chemical formula (I) or a salt thereof acceptable as drug, wherein said stabilizer mentioned in any one of claims 1-6 is mixed with a compound represented by said chemical formula (I) or a salt thereof accepted as drug.
8. A stabilizing method according to claim 7, wherein said stabilizer is tartaric acid.

9. A stabilizing method according to claim 7 or 8, wherein the quantity added of said stabilizer is not less than 0.1 weight part is mixed with 1 weight part of said compound represented by said chemical formula (I) or a salt thereof accepted as drug.
- 6 10. A stabilizing method according to claim 9, wherein the quantity added of said stabilizer is 0.3-5 weight part.
11. A stabilized drug, wherein a stabilizer mentioned in any one of claims 1-6 is mixed with a compound represented by said chemical formula (I) or a salt thereof accepted as drug.
- 10 12. A stabilized drug according to claim 11, wherein said stabilizer is tartaric acid.
13. A stabilized drug according to claim 11 or 12, wherein the quantity added of said stabilizer is not less than 0.1 weight part per 1 weight part of said compound represented by said chemical formula (I) or a salt thereof accepted as drug.
- 15 14. A stabilized drug according to claim 13, wherein the quantity added of said stabilizer is 0.3-5 weight parts.

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European
Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 91 10 4502

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. CL5)
Y,D	EP-A-0 113 108 (FUJISAWA PHARMACEUTICAL CO., LTD) * Page 1, lines 1-7; page 39, example 1; claims 7,8 * & JP-A-59 152 388 - - - -	1-14	A 61 K 31/16 A 61 K 47/12 A 61 K 47/22
Y	PATENT ABSTRACTS OF JAPAN, vol. 9, no. 145 (C-287)[1868], 20th June 1985; & JP-A-60 028 923 (TEIJIN K.K.) 14-02-1985 * Abstract *	1-14	
Y	PATENT ABSTRACTS OF JAPAN, vol. 8, no. 150 (C-233)[1587], 12th July 1984; & JP-A-59 055 828 (NITTO DENKI KOGYO K.K.) 31-03-1984 * Abstract *	1	
Y	FR-A-2 333 494 (SENJU PHARMACEUTICAL CO., LTD) * page 1, lines 1-4; page 3, lines 2-13; pages 5,6, experience 1; claims 1-3 * - - - - -	1	
The present search report has been drawn up for all claims			
Place of search		Date of completion of search	Examiner
The Hague		04 July 91	BOULOIS D.J.-M.
CATEGORY OF CITED DOCUMENTS X: particularly relevant if taken alone Y: particularly relevant if combined with another document of the same category A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons &: member of the same patent family, corresponding document			